PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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C/O ANTHONY CASTORINA
2001 JEFFERSON DAVIS HIGHWAY, SUITE 207
ARLINGTON, VA 22202

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02 AUG 2007
Applicant's or agent's file reference 27964	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL04/00644	15 July 2004 (15.07.2004)	17 July 2003(17.07.2003)

Applicant

GAMIDA-CELL, LTD

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the *PCT Applicant's Guide.*

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer /Lora E. Barnhart Telephone No. (571) 272.1600

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 27964	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL04/00644	International filing date *(day/month/year)* 15 July 2004 (15.07.2004)	Priority date *(day/month/year)* 10 May 2004 (10.05.2004)
International Patent Classification (IPC) or national classification and IPC IPC: **C12N 5/00**(2006.01),**A61K 38/00** USPC: 435/325;514/2		
Applicant GAMIDA-CELL, LTD		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16 February 2005 (16.02.2005)	18 July 2007 (18.07.2007)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Lora E. Barnhart Telephone No. (571) 272.1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL04/00644

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-96 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 97-104 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the drawings:
pages 1-3 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/figs NONE
- ☒ the sequence listing (*specify*): NONE
- ☒ any table(s) related to the sequence listing (*specify*): NONE

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL04/00644

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-41,47,48 and 50-52

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-41,47,48 and 50-52 are so unclear that no meaningful opinion could be formed *(specify)*:

Please See Continuation Sheet

☒ the claims, or said claims Nos. 1-41,47,48 and 50-52 are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL04/00644

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 43,45	YES
	Claims 42,44,46,49	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 42-46,49	NO
Industrial Applicability (IA)	Claims 42-46, 49	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 42, 44, and 46 lack novelty under PCT Article 33(2) as being anticipated by Wilson et al. The claims are interpreted as being drawn to endodermal stem cells. Wilson et al. teach isolated stem cells that express endodermal markers. It is noted that the cells are claimed as being produced by a particular method, but the manner of making does not materially affect the properties of the composition in the absence of a substantive evidentiary showing. Therefore, the cells of claim 42 read on stem cells with endodermal character made by any means.

Claim 49 lacks novelty under PCT Article 33(2) as being anticipated by any of Smith, Grant, or Jackson et al. The claims are interpreted as being drawn to endocrine hormones. Smith, Grant, and Jackson et al. teach isolated insulin, somatostatin, and glucagon. It is noted that the hormones are claimed as being produced by a particular method, but the manner of making does not materially affect the properties of the composition in the absence of a substantive evidentiary showing. Therefore, the hormones of claim 49 read on hormones made by any means.

Claims 43 and 45 lack an inventive step under PCT Article 33(3) as being obvious over Wilson et al. in view of Benvenisty. The claims are drawn to endodermal stem cells in a culture medium comprising hepatic growth factor. Wilson et al. teach endodermal stem cells, but Wilson et al. do not teach combining said cells with hepatic growth factor. Benvenisty teaches growing stem cells in a culture medium with hepatic growth factor to change the differentiation state of the stem cells. It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to culture the endodermal stem cells of Wilson et al. in the hepatic growth factor of Benvenisty in order to alter the differentiation state of said stem cells.

Claims 42-46 and 49 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:

Section III. Non-establishment of opinion (description/claims/drawings unclear)
Claims 1-41, 47, 48, and 50-52 are drawn to methods of treating cells, but the conditions recited in the claims are not adequately described in the specification to allow a meaningful search. For example, claim 1 requires culturing stem cells under conditions selected from the group consisting of conditions reducing expression and/or activity of CD38; conditions reducing the capacity of said cells to respond to CD38 pathways, retinoic acid, vitamin D, signaling pathways involving retinoic acid and vitamin D; conditions wherein cells are cultured in the presence of nicotinamide or related compounds, a copper chelator, a copper chelate, or a PI 3-kinase inhibitor, such that the stem cells expand but do not substantially differentiate. These conditions are not adequately described in the specification, because the specification does not describe each and every set of conditions in the claims such that the examiner can conduct a meaningful search for culturing stem cells under each of the conditions. While various conditions are discussed broadly (page 23, line 19, through page 36, line 29), the specification does not indicate whether any or all of them would actually yield the desired effect. The examples are limited to a single experiment in which hepatic stem cells are cultured with the heavy metal chelator TEPA or the retinoic acid agonist AGN 194310 and proliferate for "several passages" (page 88, lines 3-24). This single example does not provide adequate support for the claims across their entire scope.